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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/992,680	11/19/2001	Chi-Huey Wong	84503	1046

24628 7590 12/01/2004

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EXAMINER

PRATS, FRANCISCO CHANDLER

ART UNIT	PAPER NUMBER
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1651

DATE MAILED: 12/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

**Advisory Action**

Application No.

09/992,680

Applicant(s)

WONG ET AL.

Examiner

Francisco C Prats

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--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 12 November 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

**PERIOD FOR REPLY** [check either a) or b)]

- a) ☐ The period for reply expires \_\_\_\_\_ months from the mailing date of the final rejection.
- b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☒ A Notice of Appeal was filed on 12 November 2004. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.
2. ☐ The proposed amendment(s) will not be entered because:
- (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);
- (b) ☐ they raise the issue of new matter (see Note below);
- (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
- (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: \_\_\_\_\_

3. ☐ Applicant's reply has overcome the following rejection(s): \_\_\_\_\_.
4. ☐ Newly proposed or amended claim(s) \_\_\_\_\_ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
5. ☒ The a) ☐ affidavit, b) ☐ exhibit, or c) ☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: see attachment.
6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.
7. ☒ For purposes of Appeal, the proposed amendment(s) a) ☐ will not be entered or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

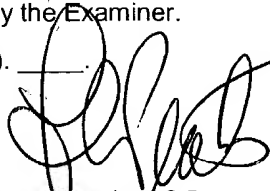
Claim(s) allowed: \_\_\_\_\_.

Claim(s) objected to: \_\_\_\_\_.

Claim(s) rejected: 21-26, 28, 29 and 52-57.

Claim(s) withdrawn from consideration: \_\_\_\_\_.

8. ☐ The drawing correction filed on \_\_\_\_\_ is a) ☐ approved or b) ☐ disapproved by the Examiner.
9. ☐ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). \_\_\_\_\_
10. ☐ Other: \_\_\_\_\_

  
Francisco C Prats  
Primary Examiner  
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**ATTACHMENT TO ADVISORY ACTION**

The after-final amendment filed November 12, 2004, has been received and entered. The Declaration of Dr. James C. Paulson under 37 CFR 1.132 has been received and considered. The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior office action.

All of applicant's argument regarding the pending grounds of rejection has been fully considered but is not persuasive of error. With respect to Schachter's separation of the fucose kinase from the pyrophosphorylase, it is unclear how that separation can possibly teach away from claims 21, 23, 26, 52-54 and 56, since none of those claims require a kinase. Because none of those claims require a kinase, applicant's "teaching away from a kinase" argument is not directed to any limitation present in the claims. Stated alternatively, the "teaching away from a kinase" argument is relevant only to those claims which actually recite a kinase. Applicant's argument in this regard ignores the full scope of all claims under examination.

With respect to those claims which do recite a kinase, contrary to applicant's argument, there is nothing in Schachter suggesting that the enzymes must be separated in order to be active. In fact, the enzymes are both active at the same neutral pH, which suggests that their reactions would be readily

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coupled in an *in vitro* synthesis system used to produce GDP-fucose according to the reaction scheme appearing after the first paragraph on page 285. The fact that Schachter experimentally demonstrates two separate enzyme reactions does not negate a reasonable expectation of coupling those enzymatic reactions when that reasonable expectation is based on the reference's explicit and plain disclosure of the overall reaction scheme. Thus, because applicant provides no factual evidence of the supposed requirement of separating the enzymes, such as an actual statement in Schachter that the two enzymes required separation for activity, applicant's argument is based on conjecture which lacks support in the actual document.

With respect to the supposed fact that Bergh's fucosyltransferase is a membrane-bound enzyme, and therefore would allegedly have been expected to interfere with the nucleoside-diphospho fucose forming enzyme recited in the claims, it is again respectfully submitted that applicant's argument lacks any substantial factual support. Applicant asserts, and provides expert opinion in support thereof in the form of the Declaration of Dr. Paulson, that the claimed fucosyltransferase enzyme and the claimed enzymes which produce substrate for the transferase are naturally present in different parts of the cell, said compartments having significantly

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different chemical conditions therein, including pH and reducing environment, and that therefore the artisan of ordinary skill would not have had a reasonable expectation that combining a fucosyltransferase with enzymes which make the fucosyltransferase's substrate would result in fucose transfer.

However, other than the expert opinion of Dr. Paulson, applicant provides no actual citation from any literature or document supporting certain critical propositions underlying applicant's argument. Applicant's argument as well as Dr. Paulson's Declaration assumes that fucosyltransferases are only present in the Golgi apparatus. No prior art is cited in support of this proposition. Applicant's argument as well as Dr. Paulson's Declaration assumes that the pH optima of the various enzymes are different, based on their natural locations within different cellular compartments. Again, however, applicant fails to provide documentation supporting this assumption. Applicant urges that because the fucosyltransferase was known to be membrane-bound, the fucosyltransferase "may interact" (page 5-6 of response of November 12, 2004) with the GDP-fucose-forming enzymes. Again, however, applicant fails to explain why this interaction would have been expected, as well as failing to provide evidentiary support for this supposedly expected interaction. Thus, applicant's argument is based on

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certain critical assumptions which applicant has not demonstrated to be true.

In fact, the facts support a conclusion other than applicant's. The fact is that all of the enzymes recited in the claimed systems were in fact known to be active at or near neutral pH. Applicant has as much admitted this in the specification. See, e.g., specification at page 17, lines 21-34. One of ordinary skill in the art clearly would have reasonably expected enzymes having similar pH optima to be usable together. Moreover, although Bergh does not explicitly disclose suitable reaction conditions of the fucosyltransferase mentioned therein, one of ordinary skill viewing Bergh would have reasonably expected the fucosyltransferase mentioned by Bergh to have functioned at a neutral pH range, based on the reaction conditions of the other Golgi-contained glycosyltransferases disclosed therein. See Bergh, e.g., sentence spanning columns 13 and 14 (pH optimum of 6.0 to 6.5 for galactosyltransferase); also at column 14, lines 54-68 (pH optimum of 6.5 to 7.0 for sialyltransferase). Further still, the GDP-fucose-forming enzymes of Schachter are also disclosed as being reactive at a neutral pH. Thus, contrary to applicant's unsupported assertions, one of ordinary skill viewing the cited references, recognizing that the various

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enzymes function at compatible pH ranges, clearly would have been motivated to have combined a fucosyltransferase enzyme with enzymes known to produce the substrate for the fucosyltransferase enzyme.

Applicant's argument with respect to the failure of the prior art to suggest "catalytic amounts" of the GDP-fucose-forming enzymes ignores the prior art and the scope of the claims. Schachter's process used enough enzyme to catalyze the production of a measurable yield of GDP-fucose. Schachter therefore clearly used a catalytic amount.

Regarding the Demain reference, note specifically that although claim 21 does not recite the presence of a pyruvate kinase, applicant is clearly aware that dependent claim 24 recites the presence of a pyruvate kinase. The reason one of ordinary skill would have been motivated to have included pyruvate kinase in a reaction system comprising GDP-fucose pyrophosphorylase and fucosyltransferase would have been to prepare the fucose-1-phosphate explicitly disclosed in the Schachter reference as being required for the production of GDP-fucose. In short, the Schachter reaction requires ATP. Demain discloses that ATP is advantageously generated *in situ* using pyruvate kinase. By disclosing the desirability of preparing ATP *in situ* with pyruvate kinase as part of a multi-enzyme

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synthetic scheme, Demain provides motivation for using the methods disclosed therein to prepare ATP for any ATP-using process, including Schachter's.

Applicant urges that the claims do not recite or require an ATP-generating system. However, the claims clearly recite a pyruvate kinase. Pyruvate kinase is part of an ATP-generating system disclosed by Demain as advantageously generating ATP *in situ* for ATP-requiring enzymatic processes. Thus, while the claims do not require or recite an ATP-generating system, the claims do not exclude such a system either. Because the claimed pyruvate kinase provides an advantageous way of providing the ATP needed to produce GDP-fucose, and ultimately for the fucosyltransferase process of Bergh, one of ordinary skill would have been motivated to have included it in a reaction system useful for preparing GDP-fucose.

Moreover, with respect to the requirement of ATP in Schachter's process, one need only look at the reaction scheme on page 285 of Schachter, which clearly recites "ATP". As to the lack of a requirement of ATP in the invention as disclosed by applicant, applicant's attention is directed to Scheme 1 on page 13 of the specification, wherein the pyruvate kinase of claim 24 is used as part of an ATP-generating system. In fact, because ATP is required for fucose kinase action, embodiments of



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the claimed reaction system reciting fucose kinase could not function without ATP. Thus, applicant's argument is entirely inconsistent with applicant's own specification.

With respect to the Yamamoto disclosure applicant again refers to subject matter being "misquoted." Yamamoto was never quoted in the final rejection or in the first office action. It is not clear how something can be "misquoted" when there was never a quote. Applicant's statement does not correctly reflect the record. Regardless, Yamamoto clearly discloses that compositions comprising the claimed ingredients, including the NADPH regenerating system, result in the production of GDP-fucose from GDP-mannose. Moreover, Yamamoto discloses that the GDP-fucose so synthesized is suitable for use as a fucosyltransferase substrate. Thus, the artisan of ordinary skill, recognizing that the GDP-fucose required in Bergh's process was suitably prepared using either Yamamoto's or Bergh's system, would have been motivated to have included the enzymes required for said syntheses in Bergh's fucosylation compositions. Moreover, the inclusion of a pyruvate kinase/PEP system in such a composition would have been obvious in view of the requirement for GTP in the synthesis of the GDP-mannose used by Yamamoto's system.

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Applicant again urges that the claims cannot be considered obvious because neither Yamamoto nor Bergh, despite the availability of the Demain and Schachter, put the claimed combinations of enzymes together. However, applicant provides no evidence that there was any long-felt need which has been alleviated by the claimed combination. Rather, on the current record, the fact that the claimed combination was never made before applicant's filing date simply cannot, from a logical or legal standpoint, demonstrate non-obviousness. Specifically, § 103(a) assumes that no single prior art reference discloses every limitation recited in the claims. Using applicant's proposed criteria of obviousness, no reference could ever demonstrate obviousness, unless it in fact anticipated the claimed subject matter. In fact, according to applicant's logic, any reference which failed to make the claimed combination would in fact be evidence of the non-obviousness of the claimed invention. This is simply not the state of the law.

Rather, the inquiry required under § 103(a) is that "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art[,]" then a patent on that subject matter cannot be obtained. Section 103(a) does not

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mention anything about how long the elements had been available to prior art practitioners. While, the age of the references may be of relevance when looking to secondary considerations of obviousness (e.g., solving a long-felt, but unsolved need), the relative age of the cited references cannot be considered evidence of non-obviousness, absent a showing that the art tried and failed to solve the same problem notwithstanding its presumed knowledge of the references. See *In re Wright*, 569 F.2d 1124, 193 USPQ 332 (CCPA 1977).

With respect to the assertion that only through hindsight would the artisan of ordinary skill have made the combination of references made in the rejection, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In the instant case applicant's claims recite an assembly of elements known to be useful in the preparation of fucosylated products. As discussed above, and in the previous office actions, the artisan of ordinary skill, recognizing solely from the prior art

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that the claimed combinations of enzymes were suitable in the preparation of fucosylated oligosaccharides, clearly would have been motivated to have assembled the claimed ingredients into a single composition. The rejections of record are therefore properly maintained.

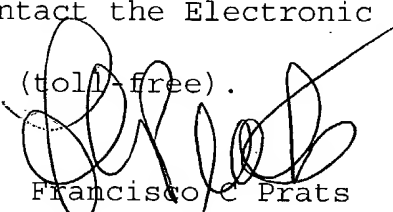
No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Francisco C Prats whose telephone number is 571-272-0921. The examiner can normally be reached on Monday through Friday, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Francisco C. Prats  
Primary Examiner  
Art Unit 1651

FCP